Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 34-39, 41-49, and 52-54 are pending in the application, with claims 1, 34, 36-37, 47, and 52 being the independent claims. Claims 40, 50, and 51 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue these claims in a divisional application. Claims 1, 34, 36-37, 43-45, 47-48, and 52-53 are sought to be amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

The specification at page 8, the paragraph at lines 15-26 from the top has been amended to more distinctly describe amended Figure 6 and to correct typographical errors. Support for the amendment is found in the original specification at page 8, lines 15-26 from the top of the page, and in original Figure 6.

Figure 6 has been amended to include alphabetical reference characters to further distinguish each graph.

Support for the amendment to claims 1 and 37 is found, *inter alia*, in the specification as originally filed at page 4, lines 19-34; page 5, lines 5-9; and page 16, lines 7-17.

Support for the amendment to claims 1, 34, 36-37, 47, and 52 is found, *inter alia*, in the specification as originally filed at page 2, line 29, through page 3, line 12; page 3, line 31, to page 4, line 3; page 15, lines 3-6; and page 9, line 29, to page 10, line 20.

Support for the amendment to claims 43-45 is found, *inter alia*, in the specification as originally filed at page 5, lines 14-23.

Support for the amendment to claim 47 is found, *inter alia*, in the specification as originally filed at page 6, lines 3-26.

Support for the amendment to claims 47, 48, 52, and 53 is found, *inter alia*, in the specification as originally filed at page 2, lines 24-27; page 3, lines 5-6; and in the originally presented claims.

Support for the amendment to claim 53 is found, *inter alia*, in the specification as originally filed at page 5, lines 2-4 and 11-13.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Requirement for Corrected Drawings

The Examiner asserts on page 3 of the Office Action that new drawings are required for Figure 6 based on alleged lack of clarity between the brief description of Figure 6 and the actual Figure 6. The Examiner states that:

> the brief description of the drawings contains references to Figures 6a-6e, and the drawings contain five graphs on the page indicated Figure 6; however, which figure is 6a, 6b, 6c, 6d, and 6e is not clear.

Office Action at page 3. Applicants note that the brief description of Figure 6 as filed does not contain references to Figures 6a-6e as asserted by the Examiner. *See* Specification as filed at page 8, lines 15-26. The brief description of Figure 6 describes "a graph depicting *mouse strain-specific differences* in transgene expression." *See* Specification at page 8, lines 15-16, emphasis added. The brief description also describes Figure 6 in terms of the "mouse strains indicated." *Id.* at line 17. Examination

of Figure 6 demonstrates that Applicants' description of "strain-specific differences" and "mouse strains indicated" is clear given that Figure 6 uses the indications "NCR NUDE, C57BL/6, Balb/c, C3H, and Rag-1" to distinguish the different mouse strains. *See* Figure 6. As is also clear upon examination of Figure 6, the lowercase alphabetical characters "a-e" are depicted on the x-axis of the graph for each strain, showing results from viral dosing as described in the brief description and not indicating individual graphs. *Id.* However, purely in the interest of furthering prosecution and not as an admission that the Examiner's assertion is correct, Applicants have amended Figure 6 such that the graphs depicting the indicated strains are additionally distinguished as FIG. 6A-6E. As such, Applicants believe the basis for the drawing objection has been rendered moot and respectfully request that the Examiner reconsider and withdraw the objection.

II. Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 47-48 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse the Examiner's rejection as it applies to the pending claims.

On page 4 of the Office Action, the Examiner stated that:

> Claim 47 is rejected because while claiming a method of modulating toxicity associated with a virally encoded transgene, only requires the administration of an agent, and does not require the administration of any virally encoded transgene. Hence it is unclear how the method is effected: i.e., there is no nexus between the claimed method and the steps of the method.

Id. In claim 47 as amended, the method requires administration of both the transgene and the agent, wherein the agent is administered prior to or concurrently with the viral

vector comprising the transgene. As such, there is a clear nexus between the claimed method and the steps of the method.

On page 4 of the Office Action, the Examiner also states that:

> Claim 48 is rejected because while requiring that the agent of claim 47 to be administered before administration of a therapeutic nucleic acid encoding a therapeutic transgene, claim 47 does not require transgene, and the method does not "further comprise" administration of such nucleic acid.

Id. As noted above, the currently claimed method of claim 47 demonstrates a clear nexus between the claimed method and the steps of the method. Additionally, currently amended claim 48 clearly depends from currently amended claim 47. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the indefiniteness rejection.

III. Claim Rejections under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 34-37, 39, 41-42, 44-49, and 52-53 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

The Examiner appears to believe that Applicants must demonstrate a core structure for a representative number of species of "agent" associated with the effects upon Kupffer cells recited in the claims at issue. Office Action, pages 5-7. Applicants respectfully submit that the Examiner misapplies current law as to the written description requirement.

Under current case law, the "representative number of species" test and the "common structural features" test of *Regents of the Univ. of Calif. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997) are inapposite when "the claim terms at issue...are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." *See Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003). This reasoning was expanded upon in *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005) where the Court of Appeals for the Federal Circuit ("Federal Circuit") made clear that there is no requirement to re-describe what is already known in the field. *Id.* at 1357.

In *Amgen,* the claimed methods included, *inter alia*, the step of "growing...vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence..." *See Id.* at 1322. Also at issue were dependent claims that specified that the cells were mammalian cells. *Id.* The defendants asserted that the claims lacked adequate written description, alleging that "Amgen failed to sufficiently describe the use of all vertebrate and mammalian cells." *See Amgen* at 1331. The Federal Circuit disagreed, maintaining that written description is sufficient when the subject matter in question is well known and fully appreciated by persons of ordinary skill in the art. *Id.* at 1332 (internal citations omitted). The Federal Circuit refused to apply the "representative number of species" test to the terms "vertebrate cells" and "mammalian cells" because those of ordinary skill in the art would readily comprehend the members of the genus. *Id.* Further, the court concluded that the claims at issue were adequately described, even though the specification described only two species within the genus vertebrate or mammalian cells. *Id.*

In *Capon*, the claimed methods included, *inter alia*, the production of chimeric genes for providing cells of the immune system with cell-surface antibodies for infiltration of disease sites. *Id.* at 1351. The Board of Patent Appeals and Interferences held that the claims were invalid, asserting that the specifications at issue failed to provide written description regarding "structure, formula, chemical name or physical properties" for the full scope of the claimed chimeric DNA or encoded proteins. *Id.* at 1354. The Federal Circuit disagreed, stating that written description requirements vary based on the invention at issue in light of "the scientific and technologic knowledge already in existence." *Id.* at 1357. In *Capon*, the Federal Circuit noted no descriptive substance would be added by requiring written description of known sequences. *Id.* at 1358. As such, written description does not require disclosure of a structure known in the field.

The Specification clearly demonstrates that Applicants were in possession of "agents" as utilized in the context of the claims at issue. Agents are described as including "viral vectors" comprised of "viral nucleic acid" in which the viral vector may be provided in a "viral particle." Such agents are specifically described as "viral nucleic acid that lacks the therapeutic nucleic acid, or lacks a nucleic acid encoding a functional copy of the therapeutic nucleic acid;" "viral particle that lacks the therapeutic nucleic acid" or that includes "a variant of the therapeutic nucleic acid that does not encode a functional protein;" and a viral particle that includes a "transgene that encodes a readily detectable marker protein." Specification at page 3, lines 13-26; page 4, lines 4-11; page 15, lines 6-15. Agents are also described as including particulate matter such as "a size that is suitable for phagocytic uptake by the Kupffer cells of a subject;" "particulate

matter whose component particles have a diameter of about 10 nm to about 1000 nm;" "particulate matter...about the same diameter as the viral vector encoding the therapeutic transgene product." Specification at page 3, lines 26-27; page 4, lines 13-18; page 15, lines 16-33. Applicants also disclose agents capable of lowering levels of Kupffer cells such as "liposomal doxorubicin." Specification, page 3, lines 27-30; and page 14, line 33, through page 15, line 2. Under the reasoning applied in *Amgen*, a "representative number of species" test is inappropriate because those of ordinary skill in the art could readily identify members of the genus "agents" as defined in the Specification. Under the holding of *Capon*, structures need not be described because the viral nucleic acids, viral particles, and particulate matter included within the definition of "agents" were widely known in the art as were agents capable of decreasing the levels of Kupffer cells, as recognized by the Examiner in the Office Action at page 16.

In view of the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the written description rejection.

IV. Claim Scope: Interpretation of Claim 47

The Examiner states in the section of the Office Action entitled "Note, RE Claim Interpretation" that because claim 47 encompasses agents that modulate Kupffer cell level **or** Kupffer cell function means "that modulation of Kupffer cell function is separate and distinct from that of modulation of Kupffer cell level," limiting the other independent claims to agents that modulate Kupffer cell function. Office Action at page 9. This is an improper interpretation of Applicants' claims and Specification. For example, the Specification states at page 3, lines 27-29: "In some embodiments, the

agent modulates Kupffer cell function by lowering levels of Kupffer cells in the subject." *Id.* As such, it would be apparent to one skilled in the art that modulation of Kupffer cell function may occur through, *inter alia*, modulation of Kupffer cell levels. As such, the independent claims comprising modulation of Kupffer cell function include modulation of Kupffer cell levels and are not limited in scope as the Examiner asserts. *See*, M.P.E.P. § 2111.01, stating that claims must be interpreted as broadly as their terms reasonably allow. Moreover, Applicants are entitled to claim in the alternative, including claims in the alternative to groups and sub-groups; such claims are fully supported by Applicants' specification. *See* M.P.E.P. § 2173.05(h). However, purely in the interest of furthering prosecution and not as an admission as to the correctness of the Examiner's assertions, Applicants have amended the claims to encompass agents that reduce uptake of therapeutic nucleic acids by Kupffer cells. It is clear from the Specification that such reduction in uptake can occur through saturation of specific or non-specific binding sites. Specification at page 3, lines 8-9; page 3, line 25, to page 5, line 3; page 5, line 32, to page 6, line 2. Moreover, one of skill would understand that reduction of Kupffer cell levels would necessarily affect the activities associated with Kupffer cell functions, including specific and non-specific uptake. *Id.* As such, the amended claims also include reduction in uptake resulting from reduction of Kupffer cells levels.

V. Claim Rejections under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 38-49, and 52-53 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

In the Office Action at page 8, the Examiner recognizes enablement for increasing the level of a therapeutic gene product in the liver of a subject by a method comprising a first adenoviral vector comprising a transgene encoding a therapeutic nucleic acid operably linked to promoter elements for expression in hepatocytes and a second adenoviral vector not comprising the transgene administered prior to or concurrently with the first adenoviral vector, with each vector administered to the liver by intravenous, intrapertioneal, or direct routes. *Id.* The Examiner also recognizes enablement for pharmaceutical compositions comprising such vectors and a pharmaceutically-acceptable carrier. *Id.*

The Examiner alleges lack of enablement for transformation of non-liver tissue and increasing the level of a therapeutic gene product in non-liver tissue, administering non-adenoviral vectors to transform liver cells or modulate Kupffer cells, administering particles other than 70-100 nm to modulate Kupffer cell function, using any route of administration for delivery to liver tissue or for transformation of liver cells, using any transgenes not operably linked to promoter elements for expression in liver cells, administering a viral vector agent different from the viral vector expressing a therapeutic product, administering adenoviral agent not encoding a functional copy of the therapeutic transgene subsequent to administering adenoviral vector encoding the therapeutic transgene, modulating toxicity associated with administration of therapeutic nucleic acid, and any modulation of Kupffer cell function being able to increase transformation or expression. Office Action at pages 9 and 20-21.

In terms of transformation and expression, the Examiner characterizes the liver as "the only enabled tissue," asserting that "Kupffer cells only act in the liver and other cells

filter out viral particles in other tissues" and that "the Artisan could not reasonably predict that by acting on Kupffer cells, transformation of any other tissue than liver could occur..." *Id.* at pages 13, 15 and 20. In contrast to the Examiner's contention, Example 5 of the Specification indicates that even without using an agent to reduce uptake by Kupffer cells, fluorescently labeled adenovirus can be detected in the spleen and lung. Specification at page 33, lines 11-15. Given the detection of virus in the spleen, Applicants performed splenectomies in mice to determine if splenic macrophages represent an additional site at which sequestration of viral vector leads to a reduction in total expression of administered transgene. Specification at page 34, lines 27-31. The results obtained indicate that absence of the spleen does not result in an increase in reporter expression as would be expected if the observed localization of viral vector in the spleen represented sequestration. *Id.* While the Examiner notes that other cells may filter out viral particles in other tissues, no evidence is offered by the Examiner to counter Applicants' data regarding the impact of splenectomy on expression. *See* M.P.E.P. § 2164.04, stating that "it is incumbent upon the Patent Office, whenever a rejection [for lack of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." In fact, it was well established at the time of Applicants' filing that "hepatic reticuloendothelial cells (Kupffer cells) constitute the largest group of fixed macrophages in mammalian organism[s] and are responsible for the phagocytosis of most circulating foreign particles including living microorganisms." Fahimi, H.D. *J. Cell Biol.* 47(1): 247-262, 242 (1970), attached herewith as Exhibit A. Based on this knowledge, one of

skill could reasonably predict that by acting on Kupffer cells, expression could *increase* in other tissues without equivalent sequestration of viral vector by macrophage populations at these other sites compensating for loss of uptake by Kupffer cells.

The Examiner also alleges non-enablement for the use of viral vectors other than adenovirus to transform liver cells or to modulate Kupffer cells, suggesting that the claims are overly broad in encompassing the use of *any* vector. Office Action at pages 9, 12-14, and 18-21. Applicants note that the claims are not directed to *all* vectors. The methods and compositions taught by Applicants involve reduction in uptake of therapeutic viral vectors by Kupffer cells, with "uptake" necessarily defining the class of vectors as those able to interact with Kupffer cells in absence of an agent. Such vectors would be apparent or readily discernable to one of skill in the art based on knowledge in the art or routine screening. *See In re Wands*, 858 F.2d 731, 736-738 (Fed. Cir. 1988). Moreover, Applicants' Specification teaches a variety of viral vectors and methods of targeting such vectors, as well as common methods of determining biodistribution of viral vectors. Specification at page 9, line 29, to page 11, line 4; page 11, line 18, to page 14, line 32; Example 1; and Example 5. As such, it would be routine for one of skill to determine whether a particular vector is capable of interactions with Kupffer cells. Ghosh *et al.*, *J. Hepatol.* 32(Suppl. 1):238-52 (2000), cited by the Examiner as support for non-enablement of non-adenoviral vectors, merely demonstrates general doubts as to targeting and expression and does not offer evidence as to lack of enablement of Applicants' specific claimed methodologies and pharmaceutical compositions involving viral vectors. Similarly, given that it would be routine for one of skill to determine whether a particular vector is capable of interaction with Kupffer cells,

the Examiner's contention that the claims are not enabled for administration of particles other than 70-100 nm to modulate Kupffer cell function is without support.

The Examiner also asserts that the claims are not enabled due to alleged "lack of reasonable predictability" associated with administration of viral vector by any route other than direct or intravenous administration for delivery to liver tissue or for transformation of liver cells. Office Action at page 14, *inter alia*. *See also* Office Action page 8, where the Examiner states that intraperitoneal administration is also enabled for administration of vector to the liver. *Id.* The Examiner suggests that adenovirus administered by intramuscular injection would fail to reach the liver because adenovirus transforms "a wide variety of tissues" and would be taken up before reaching the liver. Office Action at page 14. As support, the Examiner cites comments in Ghosh *et al.* stating that *in vitro* experiments demonstrate the ability of adenovirus to transform a wide variety of cell types. *Id.* In this regard, Applicants' Specification teaches that "[a]dministration...can be via any of the accepted modes of administration for therapeutic agents. These methods include systemic or local administration..." *Id.* at page 18, lines 10-13, emphasis added. One of skill would readily understand that administration of viral vector as defined by the Applicants would allow *either* local administration to Kupffer cells or systemic administration to Kupffer cells, such that the vector would interact with Kupffer cells in the absence of an agent. Furthermore, systemic administration can occur at sites distant from Kupffer cells by a variety of methods disclosed in Applicants' Specification and known in the art, reaching the liver despite the presence of intervening tissue. For example, the Parr Declaration (attached herewith) recites post-filing *in vivo* data demonstrating that subcutaneous administration

can be a route of systemic administration. *Id.* at paragraphs 6-10. In the Declaration, Dr. Parr discusses experimental evidence showing that subcutaneous injection of an adenoviral vector comprising the firefly luciferase transgene resulted in expression of the transgene in the liver. *Id.* In the experiment, 1×10^{11} viral particles of adenoviral vector comprising the luciferase transgene were administered subcutaneously. *Id.* at paragraph 9. Twenty-one days later, a luciferase substrate was injected and an imaging system was used to detect photon output resulting from conversion of the substrate by the luciferase transgene product. *Id.* The data show that the luciferase transgene was expressed in the liver following subcutaneous administration as demonstrated by the detection of photons associated with conversion of the luciferase substrate. *Id.* Moreover, Dr. Parr notes that:

> agents which affect Kupffer cell activity would be predicted to have an even greater effect on other routes of administration where systemic distribution of the vector is observed but at a lower level than a straight i.v injection, such as the s.c. injection and liver expression shown here.

Id. at paragraph 10. As such, the *in vivo* data provided in the Parr Declaration demonstrates that the presence of intervening tissues does not as a matter of course prevent viral vector from reaching the liver as in the Examiner's hypothetical. Similarly, the fact that other systemic, non-intravenous routes can allow for localization to the liver would suggest that an agent could increase expression of a transgene administered by such routes by reducing Kupffer cell uptake of the viral vector comprising the transgene.

The Examiner further states that the Specification does not enable "any transgenes not operably linked to expression control elements." Office Action at, *inter alia*, pages 9, 12, and 14. Applicants note that the claimed methods and compositions are directed to increasing the level of a therapeutic gene product. It is well known in the field that expression requires functional control elements, such that one of skill would

know that the claims necessarily entail operable linkage to promoter elements. Such elements are also taught in the Specification. *Id.* at page 9, line 29, to page 10, line 20. However, purely in the interests of advancing prosecution and not as an admission that the Examiner's assertions are correct, Applicants have amended the claims to directly recite that the therapeutic nucleic acids of the claimed methods and pharmaceutical compositions express the recited gene products through operable linkage to a promoter.

Given the above, the Examiner's statement that "no virally encoded transgene could be administered and have expression of such transgene" is without support. Office Action at page 14. The Examiner bases the latter statement on a contention that expression would not be possible in absence of proteins required for viral expression and maintenance. *Id.* As is readily apparent to one of skill in the art, Applicants' methods and compositions for increasing the level of therapeutic gene product and for reducing toxicity are not based on situations in which transgenes are administered as nucleic acid fragments bereft of elements required for expression. Rather, Applicants' claims make clear that the therapeutic nucleic acids are comprised within viral vectors possessing appropriate control elements.

The Examiner also asserts nonenablement in terms of administration of one viral vector as an agent and a different viral vector comprising the therapeutic nucleic acid, suggesting that filtering by Kupffer cells may differ among different viruses. Office Action at page 16. Applicants note that the Specification discusses both nonspecific and specific uptake of viral vectors by Kupffer cells. Specification at page 3, line 31, to page 4, line 3; and page 5, line 34, to page 6, line 2. Moreover, the Specification teaches that nonspecific uptake includes phagocytosis while specific uptake includes receptor

mediated uptake. *Id.* at page 5, line 34, to page 6, line 2. Applicants note that knowledge in the art at the time of filing would indicate that a large portion of administered viral particles may be taken up by Kupffer cells through nonspecific uptake. *See* Marianneau *et al. J. Virol. 73(6)*: 5201-5206 (1999), attached herewith as Exhibit B. Marianneau *et al.* show that receptor-mediated endocytosis "appeared to occur far less frequently than phagocytosis" following exposure of Kupffer cells to Dengue virus, regardless of the MOI. *Id.* at page 5201, last two sentences of second column, emphasis added, sentence bridging pages 5201 and 5203, and page 5204, second column, first paragraph. As such, one of skill could reasonably expect that one viral vector administered as an agent could bind nonspecific sites associated with phagocytic uptake, thereby preventing nonspecific binding of a different viral vector carrying a therapeutic nucleic acid. Uptake of one viral vector by Kupffer cells through nonspecific, phagocytic uptake would then, based on Applicants' teachings, lead to increased expression of a therapeutic product expressed from a different viral vector by reducing the capacity of Kupffer cells to uptake the different viral vector. While different receptors *could* be involved in *receptor*-mediated uptake of different viruses, the Examiner offers no evidence that nonspecific, phagocytic uptake by Kupffer cells would differ among viruses or that such nonspecific uptake of an agent in the form of a viral vector (or particulate matter) would fail to lead to increased expression of therapeutic product from a different viral vector. *See* M.P.E.P. § 2164.04.

The Examiner further states that the claims are not enabled because they encompass administration of agent subsequent to administration of the therapeutic nucleic acid, in contrast to Applicants' data teaching prior or concurrent administration.

Applicants believe the basis for this rejection is rendered moot given that the claims now state administration of agent prior to or concurrently with administration of the therapeutic nucleic acid.

The Examiner also states that modulation of toxicity associated with administration of virally encoded transgene is allegedly not enabled (concerning claims 47-49). Office Action at page 17. The Examiner cites Lieber *et al. J. Virol. 71(11)*: 8798-8807 (1997) as "the closest prior art" supporting his assertions regarding toxicity. *Id.* The Examiner states that

> Lieber demonstrates that while TNF elevations can be dampened by administration of galladinium chloride, which also depletes Kupf[f]er cells, IL-6 release was enhanced...the Artisan would not be able to reasonably predict that any toxicity would be reduced for any virus, because the compensating IL-6 release may more than make up for any particular beneficial effects from the loss of TNF expression.

Id., internal citations omitted. The Examiner's basis for this assertion is unclear. The results described in Lieber *et al.* do not demonstrate that increased IL-6 expression reflects an increase or maintenance of toxicity associated with TNF. Rather, Lieber *et al.* suggest that IL-6 is associated with increased hepatocyte replication (a beneficial response to liver injury). Lieber *et al.* at page 8801, bridging paragraph between first and second columns. This would indicate that increased IL-6, rather than being "compensating" for loss of TNF, is actually useful to liver cells in recovering from hepatic injury. *Id.*

Moreover, Lieber *et al.* actually show, through serum glutamic-pyruvic transaminase levels, that liver damage associated with 1×10^{10} transducing units of viral vector was decreased after Kupffer cell depletion. *Id.* at page 8800, "Liver toxicity" and at page 8799, "Materials and Methods." As such, the findings of Lieber *et al.* do not

reduce the predictability of Applicants' claimed methods as asserted by the Examiner. Instead, Lieber *et al.* and Applicants examined distinct aspects of toxicity. Lieber *et al.* examined the effect of Kupffer cell depletion associated with a fixed amount of viral vector on expression of cytokines and glutamic-pyruvic transaminase, the latter used as markers of liver damage. In contrast, Applicants teach reduction in toxicity based on the showing that reduction in uptake of viral vector comprising a transgene due to administration of an agent allows for a more linear dose-response between administered vector and expressed product. Example 1 at page 25, line 20, to page 27, line 8; Example 2, page 28, lines 8-29. Additionally, Applicants teach that disproportionate increases in transgene expression with increased amounts of viral vector are avoided with administration of agent. *Id.*

Given this, one of skill would understand Applicants' teachings as showing two different mechanisms for reducing toxicity associated with expression of a transgene. In one mechanism, toxicity associated with viral proteins can be reduced because lower amounts of vector are needed for desired levels of transgene expression. In another mechanism, undesirable toxicity associated with high levels of transgene product can be reduced because disproportional dose-responses are avoided. *Id.,* page 6, lines 3-26; and page 6, line 32, to page 7, line 4.

As such, it is further apparent that the Examiner's assertion that "any specific toxic transgene's toxicity would not be modulated" is an improper basis for non-enablement. The Examiner states that products such as "ricin" would be toxic "no matter what effects the Kupffer cells may exert." However, at issue is not whether toxicity of the product is eliminated but whether undesirable toxicity associated with *expression* of

the product is reduced. For example, in some situations, a therapeutic product may be toxic to diseased tissues as well as normal tissues. A roughly linear dose-response would allow better control of expression such that primarily diseased tissues are affected rather than normal tissues. In contrast, a disproportionate dose-response in absence of agent could lead to undesirable levels of expression of the product such that an increased amount of normal tissues are affected. Applicants' methods would allow the disproportionate response and undesirable levels of expression to be avoided. As such, the Examiner's statements regarding predictability and failure to modulate a toxic transgene's toxicity do not serve as a proper basis for a non-enablement rejection.

The Examiner alleges non-enablement for any modulation of Kupffer cell function being able to increase levels of therapeutic gene products. Applicants believe the basis for this rejection is rendered moot given that the claims now require that levels of therapeutic gene product are increased as a result of prior or concurrent administration of agent.

In the section of the Office Action entitled "The Existence of Working Examples" and "The Amount of Experimentation is Undue" the Examiner once more recites laundry lists based on the above non-enablement allegations. Office Action at pages 20-22. Applicants note that the proper basis for determining enablement by working examples does not require disclosure of all possible examples, or for that matter any at all. "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 27 USPQ2d 1510, 1561 (Fed. Cir. 1999); *See also, In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970) ("a specification need not contain a working example

if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation."). Furthermore, current USPTO practice recognizes that the question of undue experimentation is a matter of degree, and "the key word is 'undue,' not 'experimentation.'" *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), quoting *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). Knowledge in the art and Applicants' teachings demonstrate that any searching and screening associated with the use of the viral vectors encompassed by Applicants' methods and compositions would be routine to one of skill in the art.

In view of the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection.

VI. Claim Rejections under 35 U.S.C. § 102

Claims 1, 34-41, 43-46 and 52-53 were rejected under 35 U.S.C. § 102(a), as allegedly being anticipated by Tao, N., *et al. Molecular Therapy* 3(1): 28-35 (2001) (hereinafter, 'Tao *et al.*'). Applicants respectfully traverse the Examiner's rejection as it applies to the pending claims.

As M.P.E.P. § 706.02(a)(II)(C) notes:

> For 35 U.S.C. 102(a) to apply, the reference must have a publication date earlier in time than the effective filing date of the application, and must not be applicant's own work.

Id. (emphasis added).

The issue of *Molecular Therapy* containing Tao *et al.* does not display a publication date prior to Applicants' effective filing date of January 22, 2001. To the contrary, evidence shows that it was publicly available after January 22, 2001. As

support for the latter, Applicants enclose exhibits of cover pages of copies of the January 2001 issue of *Molecular Therapy* that are stamped with the dates the journal was received by four separate libraries: the British Library (UK), the Medical Library of the University of Southern California (USA), the Library of the University of Louisville, KY (USA), and the Medical Research Library of Brooklyn, NY (USA) (attached herewith as respective Exhibits C-F). The earliest date on which Applicants are aware of the journal being received was January 25, 2001, after Applicants' effective filing date of January 22, 2001. As such, Tao *et al.* does not constitute prior art with respect to the instant application given that it was not made publicly available prior to Applicant's effective filing date.

In view of the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the novelty rejection.

VII. Claim Rejections under 35 U.S.C. § 103

Claims 34 and 41-42 were rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Tao *et al.* Applicants respectfully traverse the Examiner's rejection as it applies to the pending claims.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, an Examiner must demonstrate that: (1) an Applicant's claimed invention could have been attained by either a modification of the primary reference or a combination of references based on some motivation or suggestion in the prior art, (2) there would be a reasonable expectation of success associated with the motivation or suggestion, and (3) the

reference(s) teach all the claim limitations. *See* M.P.E.P. § 2142, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As noted above, Tao *et al.* is not a proper prior art reference given that its public availability was after the effective filing date of the present application. The Examiner provides no further references for motivation or suggestion in the prior art to attain Applicants' invention as a basis of the obviousness rejection.

In view of the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the obviousness rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

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